Breast cancer molecular subsets, response marker discovery and clinical trials

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Two points

- Future breast cancer studies should be subtype-specific.
- Candidate response markers to new (and old) drugs can be studied prospectively using marker-directed phase II trial designs with early stopping rules.

Breast cancer subtypes

Imagine a gastrointestinal cancer study where all types of GI cancers are eligible for treatment.

After completion of the study, subset analysis is performed for colon, rectal, gastric, and esophageal tumor locations.

Why not include all types of breast cancers in future studies as we used to do?

- ER+, TNBC and HER2 positive cancers respond differently to various therapies
  - chemo, endocrine, trastuzumab
- Composite survival curves can be confusing and unstable.
  - Variable proportion of patients in subsets x variable efficacy of therapies in each subset
- Prognostic and response markers can be (and most that we currently have are) breast cancer subtype-specific.

Different chemotherapy sensitivity according to ER and HER2 status in neoadjuvant studies

Table 4 Pathologic complete response rates according to HER2 and ER expression

	Overall population (n = 534)	HER2-positive (n = 185)	HER2-negative (n = 429)	P^a
Overall population (n = 534)	100/534 (28 ± 3%)	35/105 (33 ± 9%)	65/429 (15 ± 3%)	0.001
ER-negative subgroup (n = 207)	72/207 (35 ± 6%)	24/68 (35 ± 14%)	48/139 (34 ± 7%)	0.02
ER-positive subgroup (n = 327)	28/327 (9 ± 3%)	11/37 (30 ± 18%)	17/290 (6 ± 3%)	0.003

ER-positive, HER-2-positive patients are almost as sensitive to chemotherapy as ER-patients, in general.

F Andre & L Pusztai: Breast Cancer Res Treat. 108:183, 2008

Impact of Recurrence Score subsets on survival and power of randomized trials

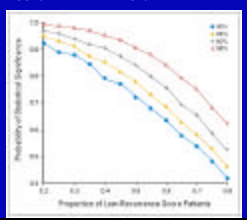
Randomized Phase III adjuvant trial for ER+ cancer

- Arm A = chemo + Tam (N=1000)
- Arm B = Tam alone (N=1000)

RS-Low 10-year DFS:	Arm A=64%	Arm B=60%
RS-Intermediate 10-year DFS:	Arm A=65%	Arm B=50%
RS-High 10-year DFS:	Arm A=55%	Arm B=45%

	Study 1	Study 2
RS-L	40%	60%
RS-I	30%	20%
RS-H	30%	20%
HR:	1.33	1.26
Power:	80%	60%

Pusztai et al JCO October 1, 2008



Proportion of patients in different RS categories in 6 studies

Study	Low Risk (RS < 18)	Int. Risk (RS 18-30)	High Risk (RS ≥ 31)
NSABP B14*	51%	22%	27%
NSABP B20*	54%	21%	25%
Kaiser controls*	56%	19%	25%
ECOG 2197**	49%	31%	20%
SWOG 8814***	40%	28%	32%
ATAC	59% (LN-)	26 % (LN-)	15 % (LN-)

Prognostic and response markers can be breast cancer subtype-specific.

- Histological grade is prognostic (and predictive of chemo response) among ER+ cancers, weak or not prognostic in ER- cancers, most ER-negative cancers are high high grade!
- Oncotype DX prognostic (+/- TAM) in ER+ cases but not useful in ER- , almost all ER- cases are high risk RS>31!
- MammaPrint prognostic in ER+, not useful in ER-, almost all ER- cases are high risk!
- Proliferation Score (signature) prognostic/predictive in ER+ cancers but not among ER-, that tend to have higher scores.
- Tau-expression, prognostic/predictive in ER+, not useful in ER- cancer all tend to have low Tau expression.

Candidate response markers have to be validated before they can be used for patient selection in a clinical trial

- This is an oximoron
- Imagine that we can only conduct a phase II study if the drug is already known to be effective in patients!

We conduct the clinical trials to find out if a drug is effective or not.

It is entirely reasonable to do same for a response marker

Tandem, 2-step Phase II trial design to rapidly evaluate a priori defined candidate predictive markers in the clinic

"Tandem 2-step phase II trial"

Develop predictor *a priori*

1. Mechanism of action
2. Preclinical models
3. Retrospective analysis

Assay must be fully defined and IDE is required

Assess in clinical trial

Pusztai L, Anderson K, Hess KR. Pharmacogenomic predictor discovery in phase II clinical trials for breast cancer. Clin Cancer Res 13:6080-86, 2007

Start with traditional, 2-step, Phase II design
Treat all comers, with early stopping rule

Few or no response

Start a second 2-step study for marker evaluation
Treat marker-positive cases only

Few or no response
Failed predictor

Some responses

Complete step 2 of the study
Potentially useful marker that defines a drug sensitive population

Some responses

Complete step 2 of the study
No pressure for patient selection

Statistical considerations

1. Define early stopping rules:

Targeted level of activity is 25% clinical benefit (CB) rate. We feel comfortable stopping the trial early if it becomes apparent that there is < 7.5% chance that this level of activity is achieved. The early stopping boundaries are:

Number of evaluated patients	*Recommend stopping if CB is ≤ than*
9	0
15	1
20	2

Probability of early termination is 80% if the true CB rate is 10%, and it is 7.5% if the CB rate is 25%.

2. Maximum sample size calculations:

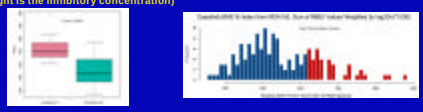
Sample size is defined by minimum CB rate and 90% credible intervals:

N	*Lower bound of CB rate*	*Upper bound of CB rate*
40	0.16	0.38
50	0.17	0.36
120	0.19	0.32

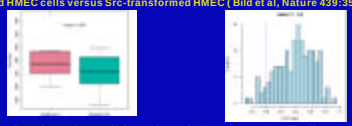
If the true CB rate is 25% with a maximum sample size of N=50, the observed CB rates would fall between 17% and 36%, 90% of the time.

Candidate predictors for dasatinib

- 1. Dasatinib inhibits at least 19 different protein kinases with high affinity (BCR-ABL, EPHA, SRC, PDGFR, KIT, LIN, FYN, YES, etc..)
  - A dasatinib target index can be calculated as the weighted average expression of all targets (the weight is the inhibitory concentration)

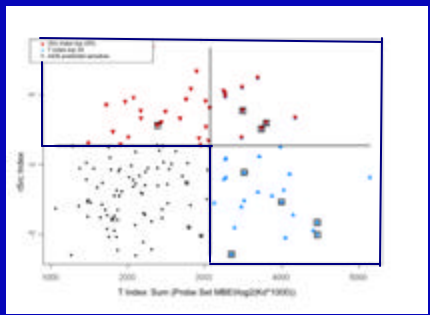


- 2. Src activation pathway consisting of 73 genes was reported
  - Compared HMEC cells versus Src-transformed HMEC (Bild et al, Nature 439:353-7, 2006)

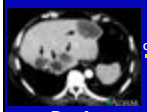


- 3. BMS has developed candidate dasatinib response predictor from in vitro data
  - Compared dasatinib-resistant versus sensitive cell lines (F Huang et al., Cancer Res 2007)

Overlap of response prediction for the 3 different predictors in human breast cancer data.



MDACC 2007-0089, Parallel, multi-arm, 2-step Phase II response marker evaluation study for dasatinib



Day 1

CT-guided FNA

CLIA lab

Day 5-7

- Dasatinib target index high → Dasatinib
- Src pathway activity high → Dasatinib
- BMS predictor score high → Dasatinib
- All scores low → OFF PROTOCOL
- Other drugs and predictors are planned

The objective is to determine if selection of patients by one of 3 a priory defined gene signatures will increase clinical benefit rate (OR + SD > 6 months) to dasatinib.

Advantages of the tandem, 2-step, Phase-II trial design

- Estimates response rates in both unselected and selected patient populations.
- Multiple predictors for the same drug can be assessed simultaneously in the same study.
- It efficiently discards candidate markers with low PPV and identifies promising markers for further validation (it also gives an idea about marker prevalence)
- Eliminates IRB obstacles for obtaining biopsies.
- Creates a unique and currently missing tissue resource.

Disadvantage

- The predictor must be fully defined a priori with cut offs and performed in CLIA environment with IDE from the FDA

Conclusions

- Future breast cancer studies may be performed separately for at least the 3 major phenotypic groups (ER+. HER2-, TNBC)
  - For ER+ cancers stratification by one of the existing molecular prognostic assays will be important in order to interpret trial results
- Candidate response markers to new (and old) drugs can be studied prospectively using marker-directed phase II trial designs with early stopping rules.

A potential synthesis of these ideas